

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte

JOHN A. KINK and KATHERINE L. WORLEDGE

Appeal 2007-3271
Application 09/832,233
Technology Center 1600

Decided: November 15, 2007

Before TONI R. SCHEINER, LORA M. GREEN, and NANCY J. LINCK,
Administrative Patent Judges.

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-5 and 7-14. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 9 are representative of the claims on appeal, and read as follows:

1. A method of treatment for necrotizing enterocolitis, comprising:
 - a) providing:
 - i) a human neonate, wherein said human neonate has symptoms of necrotizing enterocolitis;
 - ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibodies, and;
 - b) administering said formulation to said human neonate.

9. A method of treatment for necrotizing enterocolitis, comprising:
 - a) providing:
 - i) a neonate at risk for necrotizing enterocolitis,
 - ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibody, and;
 - b) administering said formulation to the lumen of the intestine of said neonate.

The Examiner relies upon the following references:

Williams	5,601,823	Feb. 11, 1997
Le	5,656,272	Aug. 12, 1997
Eibl	5,833,984	Nov. 10, 1998

Eibl et al., "Prevention of Necrotizing Enterocolitis in Low-Birth-Weight Infants by IgA-IgG Feeding," *New Eng. J. Med.*, Vol. 319, No. 1 pp. 1-7 (1988).

Wolf et al., "The anti-inflammatory effect of an oral immunoglobulin (Ig-A-IgG) preparation and its possible relevance for the prevention of necrotizing enterocolitis," *Acta Paediatr. Suppl.*, Vol. 396, pp. 37-40 (1994).

Muguruma et al., "Role of platelet activating factor in necrotizing enterocolitis development in the rat," *Prenat Neonat Med.*, Vol. 3, pp. 571-579 (1998).

We affirm.

BACKGROUND

Necrotizing enterocolitis (NEC) has emerged as the most common gastrointestinal emergency in neonatal intensive care units (NICU). A.M. Kosloske, "Epidemiology of necrotizing enterocolitis," *Acta Paediatr. Suppl.* 396:2 (1994). U.G. Stauffer, "Necrotizing enterocolitis," *Acta Paediatr* 83:666 (1994). NEC can occur endemically as isolated cases, or at times, epidemic clusters of cases are seen in neonatal nurseries. In the United States the incidence ranges from 1 to 3 per 1000 live births and roughly 1 to 7.7% of NICU admissions. R. C. Holman *et al.*, "Necrotizing Enterocolitis Mortality in the United States, 1979-85" *AJPH* 79:8 (1989). The average annual mortality rate for NEC was 13.1 deaths per 100,000 live births. In the United States, about 12,000 newborn infants per year develop NEC, with a mortality rate of up to 40%. Clinically, NEC is characterized by a triad of symptoms: abdominal distention and tenderness, gastrointestinal bleeding, and pneumatosis intestinalis, *i.e.*, air within the intestinal wall. R.M. Kliegman and A. A. Fanaroff, "Necrotizing Enterocolitis" *New Eng. J. Med.* 310:1093 (1984). Death associated from NEC occurs from intestinal perforation with sepsis with shock, intravascular dissemination, pneumatosis, and short bowel syndrome resulting in malabsorption after resection.

(Specification 1.)

The present invention is drawn to the prevention and treatment of NEC, and in particular, the use of antibody therapy (*id.* at 6). According to the Specification, it "is not intended that the present invention be limited to any particular type of antibody." (*Id.*) Thus, the Specification states "[p]olyclonal and monoclonal antibodies are contemplated in the context of the present invention. Such antibodies may be made in a variety of animals [*e.g.*, rabbits, horses, cows (*e.g.*, in the milk), and birds]. The present invention also contemplates human and "humanized" antibodies. (*Id.*) The

Specification notes that non-complement fixing antibodies, such as avian antibodies (chicken antibodies from eggs), are preferred (*id.*).

Moreover, the Specification notes that the method is not limited to antibodies to a specific inflammatory mediator, but that a variety of mediators may be used, with the preferred mediators being PAF and/or TNF (*id.* at 8). In addition, the Specification contemplates a variety of delivery preparations, such as a spray, an oral formulation, a topical formulation or an injectable formulation (*id.* at 10-11).

DISCUSSION

Claims 1-5 and 7-14 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Le, Eibl '984, Wolf, Maguruma, Eibl 1998 and Williams. Appellants argue that all the claims stand alone (Br.¹ 6). Appellants do not separately argue the claims, however, and merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable. Thus the claims stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii) (2006). We thus focus our analysis on independent claim 1.

Le is cited by the Examiner for teaching the use of anti-TNF antibodies in a number of TNF-mediated conditions, such as Crohn's disease (Answer² 4). The Examiner acknowledges that Le fails to teach the use of anti-TNF antibodies to treat neonatal necrotizing enterocolitis (NEC) (*id.*).

¹ All references to the Brief (Br.) are to the substitute Appeal Brief dated July 10, 2006.

² All references to the Answer are to the Examiner's Answer dated December 8, 2006.

Eibl '984 is cited for teaching that anti-TNF antibodies have been used to reduce the inflammatory response caused by gram-negative bacteria (*id.*). Eibl '984 is also cited for teaching that there is correlation between levels of TNF and necrotizing enterocolitis (*id.* at 4-5).

Wolf, Eibl 1998, and Magnum are all cited as evidence that the “role of TNF in the development of neonate NEC has been well established in the art.” (*Id.* at 5.)

Williams is cited by the Examiner for teaching the state of the art in formulating polyclonal avian antibodies, specifically, for treating inflammatory enterocolitis caused by *Clostridium difficile* (*id.*). The avian antibodies of Williams may be given to neonates or infants, and Williams also teaches that oral administration is a preferred route of administration (*id.* at 6).

According to the Examiner, as the role of TNF in neonatal necrotizing enterocolitis is well established in the art, it would have been obvious to use anti-TNF antibodies to treat neonatal necrotizing enterocolitis, as Le teaches the use of anti-TNF antibodies in the treatment of TNF mediated pathologies and conditions (*id.*). Because Eibl '984, Muguruma, Eibl 1998, and Wolf all teach that TNF plays a role in neonatal necrotizing enterocolitis, and Le teaches the use of anti-TNF antibodies in the treatment of TNF mediated pathologies and conditions, one of ordinary skill in the art would have had a reasonable expectation of success of treating neonatal necrotizing enterocolitis using anti-TNF antibodies (*id.*).

Furthermore, according to the Examiner, “one of ordinary skill in the art would have been motivated to formulate an avian polyclonal anti-TNF, because as suggested by Williams such type of antibodies can be

administered orally are non-immunogenic and are well tolerated by infants.”
(*Id.*)

Also, as TNF “potentiates the progress of NEC . . . reducing the effects of TNF activity among human infants would improve or alleviate the pathological changes that lead to NEC.” (*Id.*) The Examiner notes further that any alleviation of the neonatal necrotizing enterocolitis “would read on the scope of the instant claims, and the [person of] ordinary skill in the art would have had a reasonable expectation of success in at least observing some symptomatic relief when administering the anti-TNFs taught by . . . Le.” (*Id.*)

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present. We conclude that the Examiner has set forth a prima facie case of obviousness that has not been rebutted by Appellants, and affirm the rejection.

Appellants argue that Le fails to properly disclose NEC, and that even if the reference did, it would only amount to an invitation to try (Br. 9). Eibl ’984, Appellants assert, discloses inhibiting TNF- α release through the use of an IgA multimer complex that sequesters TNF- α , but does not suggest

using anti-TNF antibodies to treat NEC (*id.*). Thus, Appellants assert, Eibl '984 "teaches that necrotizing enterocolitis immunotherapy does not involve direct neutralization by specific antibodies (*i.e.*, for example, anti-TNF antibody)." (*Id.*) Wolf, Appellants argue, also does not teach anti-TNF antibody, and also "provides support for the hypothesis that immunotherapy inhibits the release of TNF- α ," and "does not involve direct neutralization by specific antibodies." (*Id.* at 9-10.)

As to Le, Appellants assert that Le teaches the use of humanized antibodies and does not teach anti-TNF antibodies of a generic nature (Reply Br. 8). Le, according to Appellants, also teaches away from enteral antibody administration, such as oral administration (*id.*). Thus, Le cannot be combined with Williams (*id.* at 11).

Eibl 1998, Appellants assert, is silent on both TNF- α and anti-TNF antibodies (Br. 10). Muguruma, Appellants assert, not only does not disclose anti-TNF antibodies, but also provides evidence "that TNF- α may not directly cause necrotizing enterocolitis." (*Id.*) Williams, Appellants contend, is silent on TNF- α and on anti-TNF antibody (*id.*). Thus, Appellants conclude, "[i]t is easily seen that the Examiner has not offered a single reference that discloses an anti-TNF antibody used for treating necrotizing enterocolitis. Consequently, on this fact alone, the obviousness rejection fails." (*Id.*)

Appellants' arguments are not convincing. Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See *In re Kuderna*, 426 F.2d 385, 389 (CCPA 1970); see also *In re Shuman*, 361 F.2d 1008, 1012 (CCPA 1966).

Appellants' arguments focus on the teachings of the individual references, and not what the prior art as a whole would suggest to the ordinary artisan.

Le teaches the use of anti-TNF antibodies in the treatment of TNF- α mediated pathologies, such as Crohn's disease (Le abstract). Le teaches the disadvantages of the use of murine monoclonal antibodies, and thus suggests using chimeric or human antibodies to overcome those disadvantages (col. 20, ll. 17-23). The preferred method of administration is parental (col. 36, ll. 17-40). Le demonstrates that the antibodies are capable of inhibiting and/or neutralizing the biological activity of TNF in vitro as well as in vivo (col. 56, Example XVI). Le exemplifies the treatment of sepsis (col. 58, Example XIX), rheumatoid arthritis (col. 58, Example XX; col. 68, Example XXII), Crohn's disease (col. 66, Example XXI), and severe ulcerative colitis (col. 78, Example XXIII).

Eibl '984 teaches treatment of inflammation with a human IgA fraction (Eibl '984 abstract). Eibl '984 teaches that deleterious inflammation occurs in diseases such as Crohn's diseases and rheumatoid arthritis (col. 1, ll. 36-46) and septic shock (col. 1, ll. 58-61). With respect to NEC, Eibl '984 teaches that "[h]igh levels of TNF- α have also been found in neonates with necrotizing enterocolitis, suggesting that TNF- α may be involved in the pathogenesis of this disease. Indeed, endotoxin challenge and administration of TNF- α has induced bowel necrosis in an experimental model of neonatal necrotizing enterocolitis." (Col. 1, ll. 62-67.)

With respect to antibody therapy, 'Eibl '984 teaches that it "is well known . . . that immunoglobulins can be useful because a specific antibody recognizes and binds to a specific antigen to neutralize that antigen." (Col. 2, ll. 40-42.) Eibl '984 also teaches that the "lethality of gram-negative

bacteremia or endotoxemia has been prevented by the administration of specific, anti-TNF antibodies.” (Col. 2, ll. 8-10.)

Wolf teaches “[i]nflammatory cytokines such as TNF- α and IL-6 play a central role in multiple effector functions and cellular interactions necessary to mount an effective host defense during inflammation and immune response,” but that “uncontrolled production leading to high levels of inflammatory cytokines may be noxious to the host.” (Wolf, p. 38, first column.) With regard to NEC, Wolf teaches that “[e]ndotoxin challenge and administration of TNF- α induced bowel necrosis in a rat model of neonatal NEC, which is predominantly mediated by PAF [platelet activating factor].” (*Id.*) Wolf uses a non-specific oral IgA-IgG preparation for the prophylaxis of NEC (*id.* at second column). Eibl 1998 is cumulative of Wolf, and thus we do not separately discuss it.

Muguruma teaches that a “number of factors known to facilitate necrotizing enterocolitis formation, such as tumor necrosis factor- α (TNF- α) and endotoxin, have been reported to increase the PAF concentration.” (Muguruma, p. 572, first column.) While recognizing a previous report in which the administration of TNF- α and lipopolysaccharide (LPS) caused necrotizing enterocolitis in an animal model, Muguruma found that in their experiments necrosis could not be demonstrated in animals receiving LPS and TNF- α , or TNF- α alone (p. 575, second column-page 576, first column). Muguruma teaches:

Others have reported that the administration of either LPS or TNF- α or the combination of both cytokines caused necrotizing enterocolitis in the rat, as judged by both gross and microscopic examination. Although we were successful in producing a full thickness hemorrhage by the treatment with these agents, a clearly identifiable necrosis was not evident The severe

hemorrhage, similar to that found in necrotizing enterocolitis, was completely prevented by treatment with r-PAF-AH. It is not clear at present why the necrosis did not develop as previously reported. If the hemorrhage is associated with the subsequent development of necrosis in all these cases, r-PAF-AH pretreatment clearly prevents its development.

(P. 578, first column.)

Thus, Le teaches that TNF- α related pathologies, such as inflammatory conditions, may be treated with a specific, anti-TNF antibody, and Eible '984, Wolf, and Muguruma establish that NEC is an inflammatory condition that is a TNF- α related pathology. Eibl '984 further provides evidence of the state of the art in antibody therapy at the time of filing. Thus, it would have been obvious to one of ordinary skill in the art at the time of filing to use an anti-TNF antibody to treat NEC.

With regard to the use of avian polyclonal antibodies, Williams teaches an avian antitoxin directed to Clostridial toxin (Williams abstract). Williams teaches that avian antitoxin (*i.e.*, avian polyclonal antibodies) does not fix mammalian complement, and thus will not cause a complement-dependent reaction, and will not exhibit complement-related side-effects (col. 9, l. 64-col. 10, l. 8). Hens laying eggs transport immunoglobulin to the egg yolk (IgY) in concentrations equal to or greater than that in serum, and the volume of egg yolk greatly exceeds that in serum (col. 10, ll. 10-18). Williams teaches further that antibody from egg is purer and more homogenous, there is less non-immunoglobulin protein, and only one class of immunoglobulin is transported to the yolk (col. 10, ll. 19-22). Williams also teaches that infant formula may be used to deliver the antitoxin (col. 12, ll. 4-5).

Thus, one of ordinary skill at the time of filing would have been aware of the advantages of using avian polyclonal antibodies and that such antibodies could be delivered in infant formula, thus it would have been obvious to use avian polyclonal antibodies as the source of anti- TNF- α antibodies.

Appellants argue further that there is no motivation to combine the references (Br. 11). According to Appellants, the teachings of Eibl '984 regarding IgA "are contrary to the teachings" of Wolf and Eibl 1998 (*id.*). Specifically, Eibl '984 teaches that it is preferable to use IgA free of IgG as IgG appears to enhance inflammatory activity (Br. 11 (citing Eibl '984, col. 6, ll. 31-34)).

Appellants argue further that Eibl '984 teaches away from the claimed invention by teaching "that a non-specific antigen/antibody interaction is the preferred approach to immunoprotection against necrotizing enterocolitis." (Br. 11.) Specifically, Appellants quote Eibl '984 as teaching that "[t]his effect [when using IgA/IgG] is believed to be a result of the formation of antigen-antibody complexes caused by high titers of antibodies against a multitude of potential pathogens and their toxins." (Br. 11 (quoting Eible '984, col. 2, ll. 24-27)). Appellants assert that "the Examiner's assumption that an unstimulated crude fractionated IgA-IgG plasma preparation is equivalent to anti-TNF antibody (as described in the Applicants' specification) demonstrates a basic misunderstanding of Applicants' claimed embodiment and is contrary to level of skill in the art." (Br. 11.)

Appellants assert that the Examiner has failed to point to any statement in the combination that would suggest or motivate the ordinary

artisan to use anti-TNF antibodies to treat NEC, and thus the rejection must fall (*id.* at 11-12).

As to the specific question of “teaching away,” a reference may be said to teach away when a person of ordinary skill, upon examining the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). In the instant case, Eibl ’984 is limited to the use of non-specific IgA, which Eibl ’984 teaches is different “from the well-known model of antibody neutralization of specific foreign antigens.” (Eibl ’984, col. 5, ll. 25-29.) Moreover, in view of the teaching of Le that anti-TNF- α may be used to treat TNF- α mediated pathologies, the ordinary artisan would not have been led in a divergent direction from that taken by Appellants in view of the teachings of Eibl ’984. Finally, avian polyclonal antibodies are IgY, not IgG, thus the argument is not relevant to the method of the combination.

As to motivation to combine, the Supreme Court in *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teaches of multiple references; the effects of demands of the marketplace; and the background knowledge possessed by a person of ordinary skill, “all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed.” *Id.* at 1740-41. Moreover, the “obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, or motivation, or by overemphasis on then importance of published articles and explicit content of issued patents.” *Id.* at 1741. Finally, one “of the ways in

which a patent's subject matter can be proved obvious is by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

In the case before us, NEC was a known pathology, and was known to be "a major life-threatening illness in neonates of low birth weight and/or low gestational age." (Wolf, p. 37, first column.) Eibl '984, Wolf, and Muguruma all establish that NEC is an inflammatory condition that is a TNF- α related pathology. Le teaches that TNF- α related pathologies, such as inflammatory conditions, may be treated with a specific, anti-TNF antibody, and Williams teaches the advantages of using avian polyclonal antibodies, which antibodies were specific to a toxin, and also teaches that the antibodies may be administered in infant formula. Thus, the method of instant claim 1 would have been obvious to the ordinary artisan at the time of filing in view of the teachings of the references cited by the Examiner.

Appellants also argue that the combination does not provide a reasonable expectation of success of achieving the claimed invention (Br. 12). According to Appellants, citing *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), "the Federal Circuit requires any reference asserted for an 'expectation of success' to *explicitly predict* that the recited claims will work." (Br. 13 (emphasis in original).)

According to Appellants, the Examiner is speculating without facts (*id.*). Appellants assert that Eibl '984, Wolf, and Eibl 1998 all teach preparations of IgA and IgG that are merely fractionated plasma extractions, whereas production on anti-TNF antibodies requires immunization procedures (Br. 13). As those references do not teach immunization,

Appellants argue that they cannot explicitly predict the success of using anti-TNF antibodies (*id.*).

It is submitted that Appellants are advocating an improper standard of the expectation of success required by an obviousness rejection.

Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co.*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed.Cir.1984); *In re Papesch*, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under § 103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

O'Farrell, 853 F.2d at 903-04.

Thus, all that is required is a reasonable expectation of success, which is provided by the combination. Le teaches the treatment of a wide variety of TNF- α related pathologies, and Williams teaches the use of polyclonal antibodies to successfully target toxins produced by *Clostridium*. In addition, Eibl '984 provides evidence of the state of the art by teaching that it is well known that immunoglobulins can be useful because a specific antibody recognizes and binds to a specific antigen to neutralize that antigen, and that the lethality of gram-negative bacteremia or endotoxemia has been prevented by the administration of specific, anti-TNF antibodies. The fact that Eibl '984, Wolf, and Eibl 1998 do not teach immunization is irrelevant

as they teach the use of IgA/IgG fractions in treating, as both Le and Williams teach immunization.

Appellants also argue that the link between TNF- α and NEC is not well established (Reply Br.³ 6). Eibl '984, Appellants assert, only states that TNF- α may be involved with NEC, thus the reference is clearly speculating (*id.* at 5). Wolf provides further evidence that the link between NEC and TNF- α is uncertain, by stating that the release of mediators of inflammation, such as TNF- α , has been implicated in NEC (*id.*). Finally, Appellants assert that Muguruma administers a combination of TNF- α and lipopolysaccharide, but NEC was not observed, and Muguruma never administers TNF- α alone (*id.*).

First, it is not clear that this argument is properly before us, as it was first presented in the Reply Brief, and does not appear to be in response to a new argument of the Examiner. Notwithstanding that, we also find this argument is not convincing. The use of the terms “may” and “implicated” are often used in scientific communications, and one of ordinary skill would not read them as stating that the link between TNF- α and NEC is tenuous.

As noted above, Eibl '984 goes on to teach that endotoxin challenge and administration of TNF- α has induced bowel necrosis in an experimental model of neonatal necrotizing enterocolitis. Wolf also teaches that endotoxin challenge and administration of TNF-alpha induced bowel necrosis in a rat model of neonatal NEC. As to Muguruma, Appellants are reading that example of Muguruma out of context of the reference as a whole. Muguruma recognizes that previous studies in which the administration of TNF- α and lipopolysaccharide (LPS) have caused

³ All references to the Reply Brief (Reply Br.) are to the Reply Brief dated May 3, 2007.

necrotizing enterocolitis in an animal model. As to their results, Muguruma states that it "is not clear why the necrosis did not develop as previously reported," but states further that the hemorrhage observed may be "associated with the subsequent development [of necrosis] in these cases." (Muguruma, p. 578, first column.) Thus, the ordinary artisan, would not understand Muguruma as casting doubt on the association between the link between TNF- α and NEC, especially in view of the teachings of Eibl '984 and Wolf.

Finally, we note that the Specification discloses that the prior art recognizes the link between TNF- α and NEC. Specifically, the Specification teaches:

Recent studies have suggested that certain proinflammatory molecules including PAF, LPS and cytokines such as, TNF and IL-6 play an important role in the development of NEC in the newborn. Patients with NEC were reported to have higher levels of TNF, IL-1 and IL-6. D. Birk *et al.*, "Is the elimination of endotoxin and cytokines with continuous lavage an alternative procedure in necrotizing enterocolitis?" *Acta Paediatr Suppl.* 396:24 (1994). Animal models for NEC indicate that the pathology associated with NEC can be generated by the administration of PAF, as well as various endotoxins and cytokines. W. Hsueh et al, "Platelet-activating factor: an endogenous mediator for bowel necrosis in endotoxemia," *FASEB J.* 1 :403-405 (1987). X. Sun and W. Hsueh, "Bowel Necrosis Induced by Tumor Necrosis Factor in Rats Is Mediated by Platelet-activating Factor," *J. Clin. Invest.* 81: 1328 (1988).

(Specification 4.)

CONCLUSION

In summary, we find that the Examiner has set forth a prima facie case of obviousness that has not been rebutted by Appellants. Thus the rejection of claims 1-5, and 7 under 35 U.S.C. § 103(a) over the combination of Le, Eibl 984, Wolf, Muguruma, Eibl (1998) and Williams, is affirmed.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

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